SPECIALTY PAPERS. There are hundreds of uses for paper and as many hundreds of types produced, all classified according to their broad use (Table 5.4). Special industrial papers are those not falling into the specific broader-use categories, and among them are the following: cigarette; filter; glassine; food containers such as paper plates, cans, cups, and wrappers coated with plastic or aluminum foil to preserve flavor and texture, prevent contamination, or inhibit moisture; Sanfordized bag material called Clupak; vegetable parchment; wallpaper and surface-waxed paper. Papermakers are currently working with textile manufacturers to develop paper suitable for disposable surgical gowns and bed sheets. Specialties are now available in the synthetic-paper field.[19] Nonwoven "cloth" is now of considerable importance[20] for a wide variety of uses in the hospital, industry, and home. Many such materials contain plastics in addition to wood fibers. Costs are substantially lower than for conventional woven cloth.

STRUCTURAL BOARDS

The classification of boards[21] made from wood particles is not standardized in the United States, and the terms fiberboard, particleboard, flakeboard, and oriented board all frequently refer to particle boards.

Fiberboards are rigid and semirigid sheets formed by the wet- or dry-felting of fibers. The low-density kinds are generally used for insulation. The new medium-density types go mainly into furniture, and the high-density types into furniture and paneling. The fiber used is usually from soft- or hardwoods, cull timber, and mill residues, and the wood is pulped by mechanical, thermomechanical, or explosive processes. A small amount of adhesive, generally phenol-formaldehyde resin, is used—particularly with dry-felted boards. Treatment to improve flame resistance or water resistance or to protect against insect damage and rot is common.

Particleboard manufacture uses sawdust, shavings, and wood flakes of special shapes to combine good physical properties with attractive appearance. Synthetic resin adhesives and different pressing conditions give varying density, strength, and surface embossing. Boards with resin adhesives are high strength and can be made with predetermined engineering properties. They have their basic elements aligned substantially in one direction. Particleboards are used for subflooring, core stock for veneered furniture, and decorative paneling and are replacing plywood and lumber for some structural applications.

Paper-base laminates are multiple sheets of resin-treated paper bonded together under high pressure and heat; under these conditions they become rigid and have no characteristics of paper. Depending on the process used, these products are termed resin-filled or resin-impregnated. They possess several characteristics, such as stability and strength, among others, which make them useful in the building industry. Other types of polymer-modified materials are listed in Chap. 34.

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[19]Polymers Roll into Printing Paper Markets, *Chem. Eng.* 78 (6), 62 (1971); Bumpy Road Ahead for Synthetic Paper, *Chem. Eng. News* October 23, 1972, p. 13.

[20]Nonwovens Symposium, *Tappi* 58 (5) 38 (1975); Gould, *Specialty Papers*, Noyes, Park Ridge, N.J., 1976.

[21]Symposiums on Particleboard, Washington State University, 1970–1975.

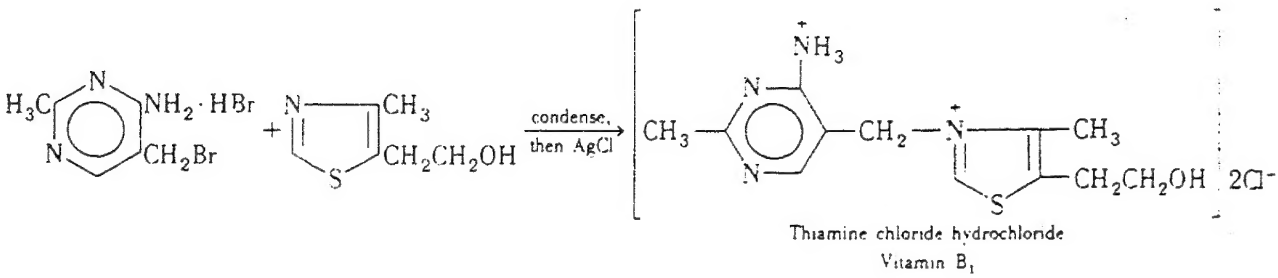
***Table* 6.3** Germicidal Activity of Certain Disinfectants in the Presence of Organic Matter

Disinfectant	*Eberthella typhosa*				*Staphylococcus aureus*			
	No Organic Matter Added		With 10% of Horse Blood		No Organic Matter Added		With 10% of Horse Blood	
	Effective Dilution	Phenol Coefficient	Effective Dilution	Phenol Coefficient	Effective Dilution	Phenol Coefficient	Effective Dilution	Phenol Coefficient
Phenol	1:90	1.0	1:80	0.9	1:60	1.0	1:50	0.8
Cresol compound USP	1:180	2.0	1:90	1.0	1:90	1.5	1:50	0.8
Cresylic disinfectant (stated phenol coefficient 5)[a]	1:500	5.5	1:150	1.6	1:250	4.1	1:70	1.1
Fortified cresylic disinfectant (stated phenol coefficient 5)[b]	1:500	5.5	1:150	1.6	1:250	4.1	1:70	1.1
Orthophenylphenol 15% disinfectant (Saponaceous)	1:600	6.6	1:120	1.3	1:200	3.3	1:20	0.3
Synthetic phenolic disinfectant (stated phenol coefficient 10)[c]	1:950	10.5	1:150	1.5	1:300	5.0	1:35	0.5
4-Chlorophenylphenol 8% disinfectant[d]	1:500	5.5	1:80	0.9	1:700	11.6	1:12	0.2
Pine oil disinfectant (stated phenol coefficient 4)[e]	1:225	2.5	1:250	2.7	1:20	0.3	1:20	0.3
Chlorine disinfectant I[f]	1:130	1.4	0	0	1:110	1.8	0	0
Chlorine disinfectant II[g]	1:600	6.6	1:3	0.03	1:400	6.6	1:1	0.01
Quaternary ammonium disinfectant I[h]	1:12,000	133	1:70	0.8	1:20,000	333	1:3,500	58
Quaternary ammonium disinfectant II[i]	1:27,000	300	1:3,000	33	1:10,000	166	1:4,500	75

Nature of tabulated disinfectant: [a]51% cresylic acid solubilized by soap; [b]26% cresylic acid, 9% *o*-phenylphenol solubilized by soap; [c]10% *o*-phenylphenol, 4% *p*-tert-amylphenol solubilized by soap; [d]8% solubilized by soap; [e]76% pine oil solubilized by soap; [f]0.48% average chlorine; [g]5.25% average chlorine; [h]hydroxydecenyldimethylethyl ammonium bromide; [i]benzalkonium chloride, aqua.

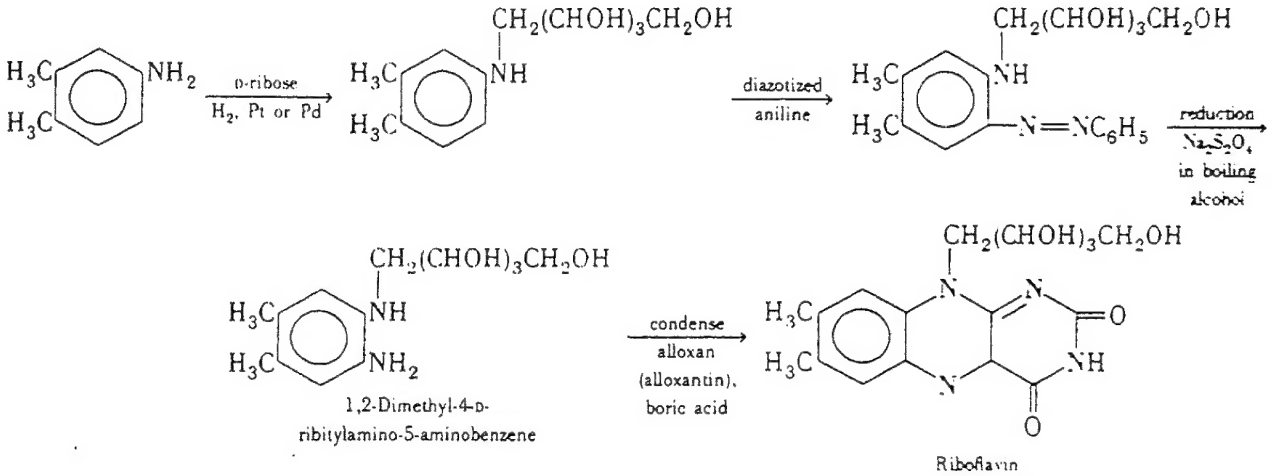
SOURCE: *Soap Sanit. Chem.*, February 1944, has more details and more extensive tables.

ylthiazole, which results in thiamine chloride hydrochloride. The last step is:



Thiamine chloride hydrochloride
Vitamin B_1

RIBOFLAVIN USP, VITAMIN B_2.[20] Riboflavin is a necessary element of all living cells. It is quite stable except under excessive exposure to light. It is considered to be the growth factor of the vitamin B_2 complex and is added on a large scale to bread, flour, and other dietary and pharmaceutical preparations. It is also involved in the transfer of oxygen to tissues. This vitamin is produced as a by-product of the butanol-acetone fermentation of molasses and by synthesis starting with 1,3,4-xylidine, D-ribose, aniline, and alloxan.



1,2-Dimethyl-4-D-ribitylamino-5-aminobenzene

Riboflavin

DEHYDRATION

ETHER USP. Ether is used for general anesthesia and as a solvent. Ether and nitrous oxide, both anesthetics, are manufactured through dehydration reactions. The very simple and long-used manufacturing procedure for ether has been the dehydration of alcohol (denatured with ether) by sulfuric acid. The anesthetic ether is especially purified and packaged. Much ether, both USP and commercial grades, is now supplied as a by-product from the manufacture of alcohol from ethylene (see Chap. 38).

HALOGENATION

Halogenation, generally chlorination, is used extensively as a chemical step in the manufacture of various intermediates, such as ethyl chloride or bromide, and homologs employed in

[20]RPS XVI, p. 961; *McGraw-Hill Encyclopedia of Science and Technology*, 5th ed., vol. 11, McGraw-Hill, New York, 1982, p. 652.

in the manufacture of finished pharmaceutical products. In only a few cases does the chlorine remain in the finished product. One such compound is chloroform. Chloroform was once employed as an anesthetic by inhalation, but now is used only rarely in the United States. It is used as a solvent for alkaloids and other organic chemicals, in chemical analysis, and as a preservative during aqueous percolation of vegetable drugs, preventing bacterial decomposition.

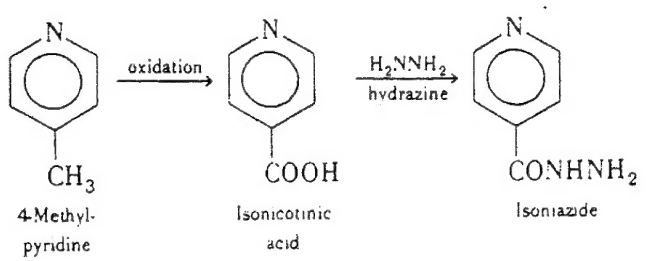
CHLOROFORM USP.[21] Although alcohol and chlorinated lime were formerly used to make chloroform, it is now made from acetone and calcium hypochlorite because the reaction is more rapid and the yield is high.

$$\underset{\text{Acetone}}{2CH_3COCH_3} + \underset{\substack{\text{Calcium}\\\text{hypochlorite}}}{3Ca(OCl)_2} \rightarrow \underset{\text{Chloroform}}{2CHCl_3} + \underset{\substack{\text{Calcium}\\\text{acetate}}}{Ca(C_2H_3O_2)_2} + \underset{\substack{\text{Calcium}\\\text{hydroxide}}}{2Ca(OH)_2}$$

Absolutely pure chloroform decomposes readily on storing, particularly if exposed to moisture and sunlight, to yield phosgene and other compounds. The USP requires the presence of a small amount of alcohol to retard this decomposition (0.5 to 1%).

OXIDATION[22]

ISONIAZID USP. Isoniazid, isonicotinic acid hydrazide, is the most potent and selective of the tuberculostatic antibacterial agents.



NICOTINIC ACID USP AND NICOTINAMIDE USP. Nicotinic acid and nicotinamide are known as niacin and niacinamide in the food industry. Niacin is the most stable of all vitamins and is essential to humans and animals for growth and health. In the body, niacin is converted to niacinamide, which is an essential constituent of coenzymes I and II, which are involved in the oxidation of carbohydrates. It is often added to foods, as in enriched flour. Niacin and niacinamide are nutritionally equivalent, and compete with one another. In the past methylethylpyridine was oxidized with nitric acid to yield niacin, and β-picoline was treated with air and ammonia to produce the nitrile which was then hydrolyzed to niacinamide. A new process can produce both niacin and niacinamide from a single feedstock, either β-picoline or 2-methyl-5-ethylpyridine by oxidative ammonolysis, a combination of oxidation and amination.[23]

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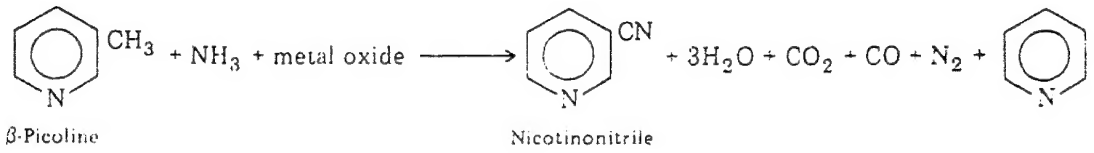
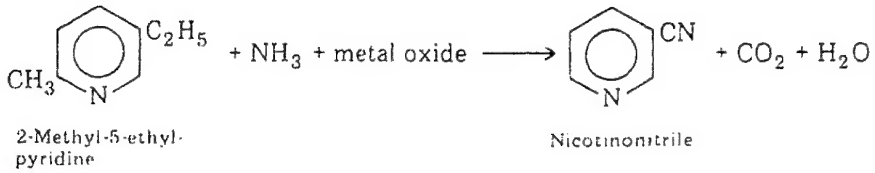
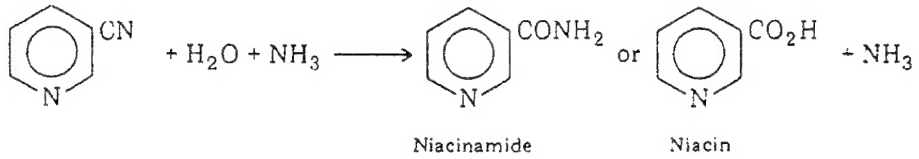
[21]RPS XVI, p. 1259.

[22]Groggins, op. cit., pp. 486–554.

[23]Paustian, Puzio, Stavropoulos, and Sze, A Lesson in Flow Sheet Design; Nicotinamide and Acid, *CHEMTECH* 11 (3) 174 (1981).



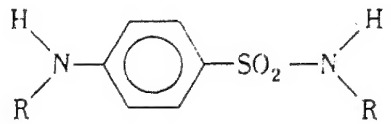




Either the acid or niacinamide can be selectively isolated from the hydrolysis by varying the hydrolysis time and nitrile concentration. Production of niacin is favored by a higher hydrolysis temperature.

SULFONATION[24]

The outstanding drugs made by sulfonation are sulfanilamide, sulfadiazine, sulfaguanidine, and sulfathiazole. Sulfanilamide, the original member of this class, is a very interesting chemical, long known as an intermediate in the manufacture of an orange-colored dye, Prontosil, before its antibacterial properties were recognized.[25] It was ascertained in 1935 that sulfanilamide (*p*-aminobenzenesulfonamide) was the active antimicrobial part of the dye. About 3300 sulfonamides have been synthesized, but only a few have passed the careful testing of the pharmaceutical industry and clinicians. The following structure characterizes all therapeutically useful sulfanilamides:



The sulfa drugs have been largely replaced by antibiotics because the sulfas have relatively narrow antibacterial spectra, comparatively low potency, and cause rapid development of resistant organisms and many adverse side effects in humans. They are often used as diuretics.

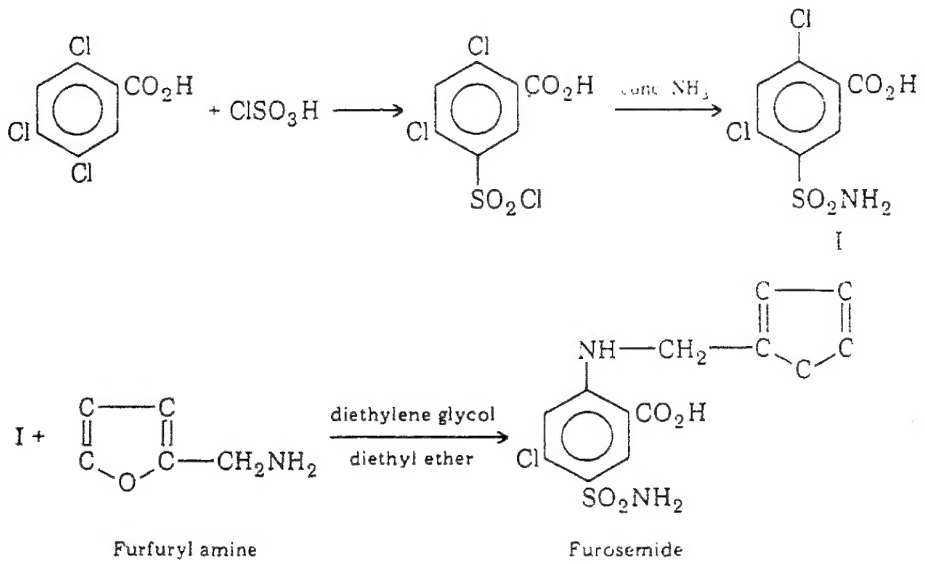
FUROSEMIDE.[26] Furosemide, 4-chloro-N-furfuryl-5-sulfamoyl anthranilic acid, is prepared by treating 2,4,5-trichlorobenzoic acid with chlorosulfonic acid, and further treatment with

[24]Groggins, op. cit., pp. 303–389; Gilbert, *Sulfonation and Related Reactions*, Interscience, New York, 1965.

[25]RPS XVI, p. 1116.

[26]RPS XVI, p. 883; Sittig, op. cit., p. 295.

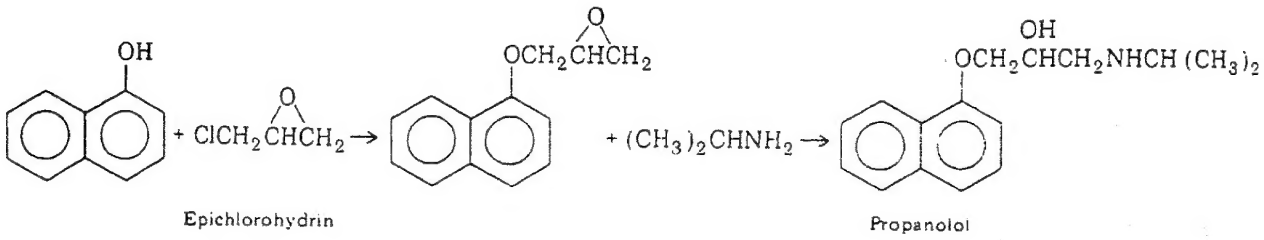
ammonia and furfuryl amine. This is a very potent diuretic and was the fifth most prescribed medicine in 1981.



AMINATION[27]

Many chemicals used as drugs contain one or more amine groups. These may be introduced into the compound by using ammonia or an amine.

PROPANOLOL·HCl.[28] This compound, sold under the tradename Inderal, was the second most widely prescribed drug in 1981. It is used as an antianginal and antihypertensive drug and is prepared from 1-naphthol and epichlorohydrin. Subsequent treatment with isopropyl amine opens the epoxy ring to yield propanolol. Treatment with HCl yields the hydrochloride.



COMPLEX CHEMICAL CONVERSIONS

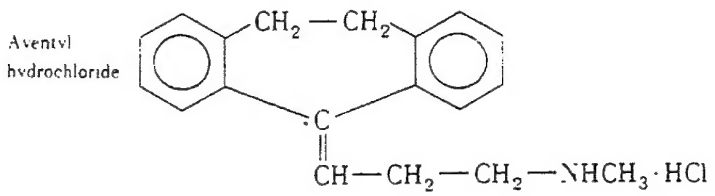
Many pharmaceutical chemicals are subjected to repeated, and often difficult, chemical reactions in order to obtain the desired product. Such conversions may be exemplified by ascorbic acid, chloramphenicol, and Aventyl HCl.[29] The latter, as an antidepressant, demonstrates this complex development. Twenty-six different chemicals are required to place the drug's 43 atoms in their precise molecular pattern in a six-step manufacturing process starting from

[27]Groggins, op. cit., pp. 388–485.

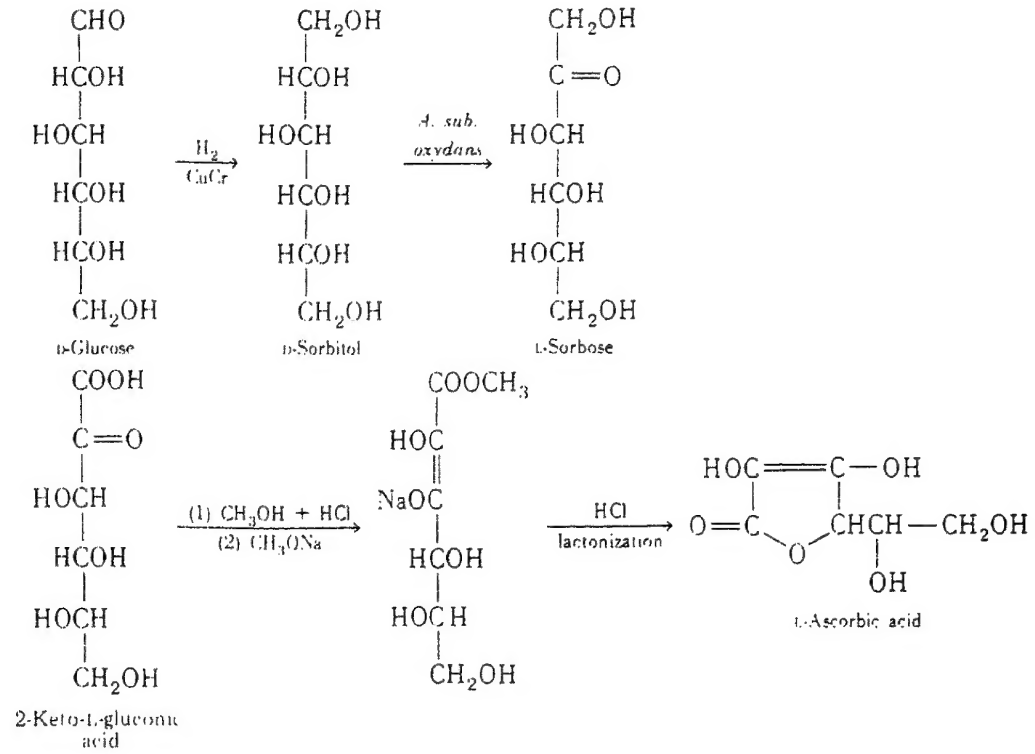
[28]RPS XVI, p. 845; Lednicer and Mitscher, op. cit., p. 117.

[29]Peters and Hennion, Synthesis of Nortriptyline, *J. Med. Chem.* 7 390 (1964).

phthalic anhydride. Its formula is



ASCORBIC ACID USP, VITAMIN C.[30] Vitamin C is often called the antiscorbutic vitamin. It is also needed in wound and bone healing and is a factor in resisting infection. Much of this vitamin is supplied in foods, especially fresh citrus fruits, tomatoes, and green vegetables. Ascorbic acid in solution or in foods is unstable, but the contrary is true if it is in dry form (powder or tablets). All the ascorbic acid used commercially is synthesized; 14.5×10^3 was produced in 1981. It is produced from glucose by these reactions:



DARVON. Darvon (Lilly), *d*-propoxyphene HCl, is a synthetic, nonantipyritic, orally effective analgesic, similar pharmacologically to codeine. "It is approximately equal milligram for milligram to codeine in analgesic potency, produces no respiratory depressions, and has little or no antitussive activity."[31] It is unique in that it is not a narcotic yet can be substituted for codeine, and is useful in any condition associated with pain. This analgesic is not analogous *chemically* to codeine or morphine. It was discovered and synthesized commercially in the Lilly laboratories. Its synthesis starts with relatively simple chemicals, but many steps are involved in its manufacture. These are outlined in the following *chemical conversions*. The second step is detailed and illustrated in Fig. 6.4.

[30]RPS XVI, p. 995; *McGraw-Hill Encyclopedia of Science and Technology*, 5th ed., vol. 1, McGraw-Hill, New York, 1982, p. 745.

[31]RPS XVI, p. 1061; Lednicer and Mitscher, op. cit., p. 50.

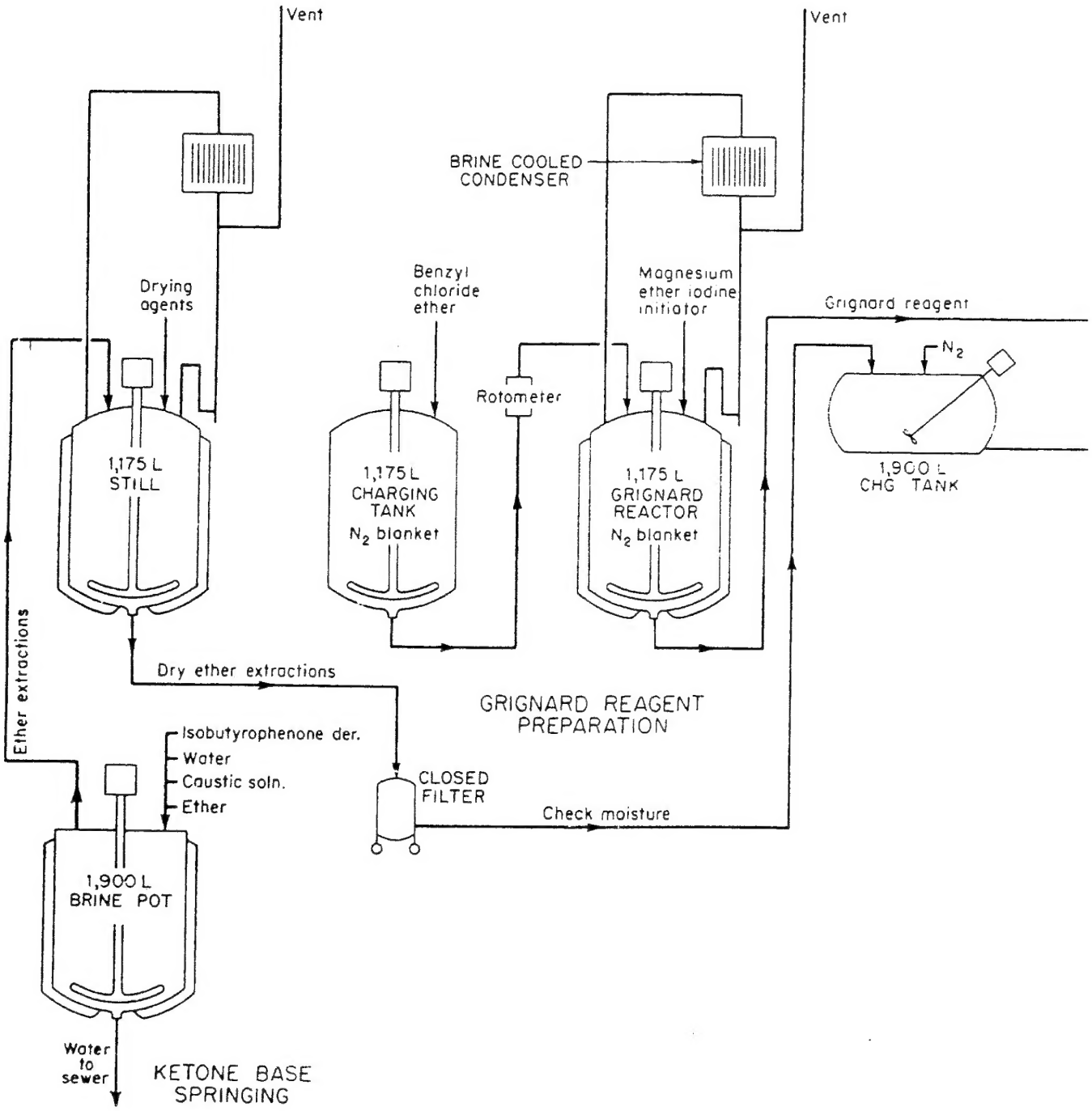
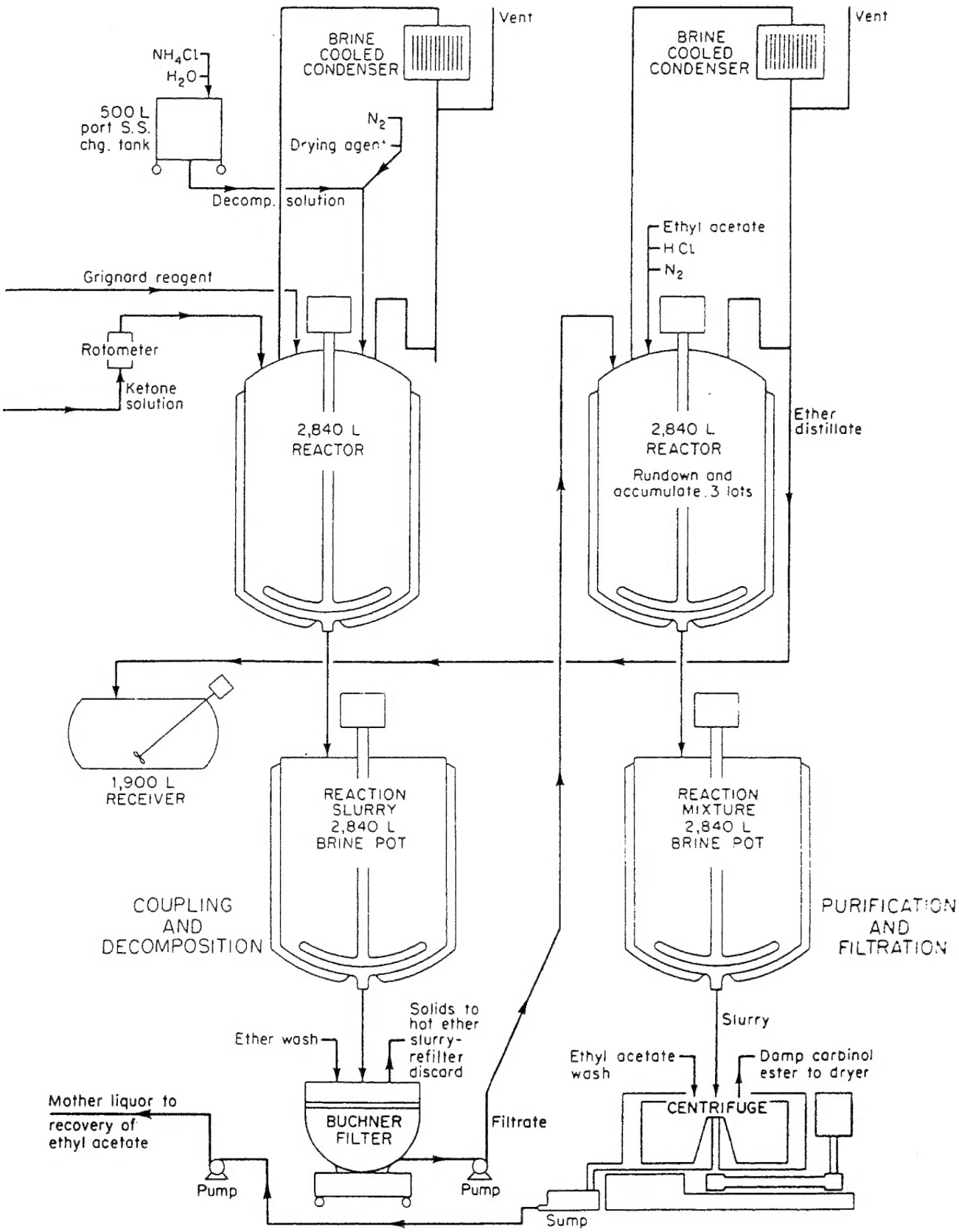
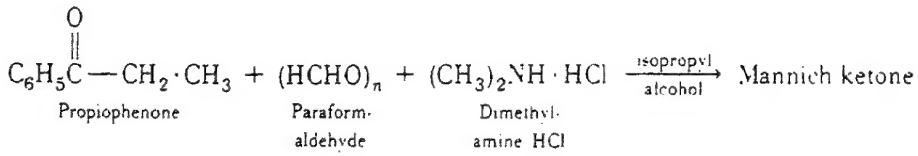


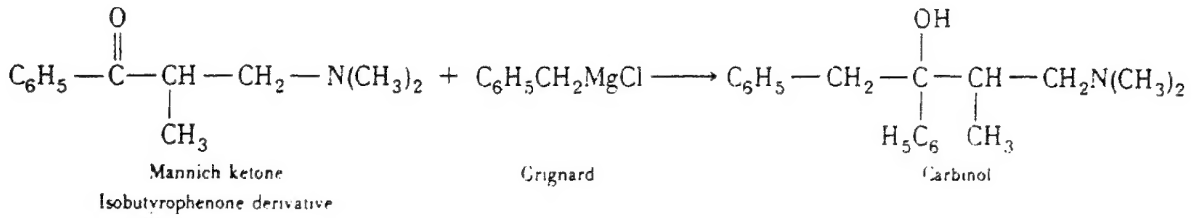
Fig. 6.4. Darvon production flowchart, showing equipment involved in step 2 described in the text. *(Eli Lilly & Co.)*


BRINE COOLED CONDENSER
Vent
BRINE COOLED CONDENSER
Vent
NH_4Cl
H_2O
500 L port S.S. chg. tank
N_2
Drying agent
Decomp. solution
Ethyl acetate
HCl
N_2
Grignard reagent
Rotometer
Ketone solution
2,840 L REACTOR
2,840 L REACTOR
Rundown and accumulate 3 lots
Ether distillate
1,900 L RECEIVER
REACTION SLURRY 2,840 L BRINE POT
REACTION MIXTURE 2,840 L BRINE POT
COUPLING AND DECOMPOSITION
PURIFICATION AND FILTRATION
Solids to hot ether slurry-refilter discard
Ether wash
Slurry
Ethyl acetate wash
Damp carbinol ester to dryer
Mother liquor to recovery of ethyl acetate
BUCHNER FILTER
Filtrate
CENTRIFUGE
Pump
Pump
Sump

Step 1. Coupling to give a Mannich ketone.



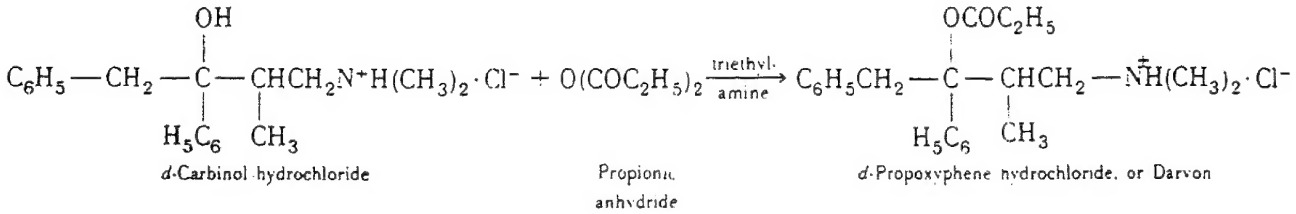
Step 2. Coupling Mannich ketone with benzyl chloride, using Grignard technique (and decomposition).



Step 3. Resolution of optical isomers by the use of *d*-camphorsulfonic acid in acetone.

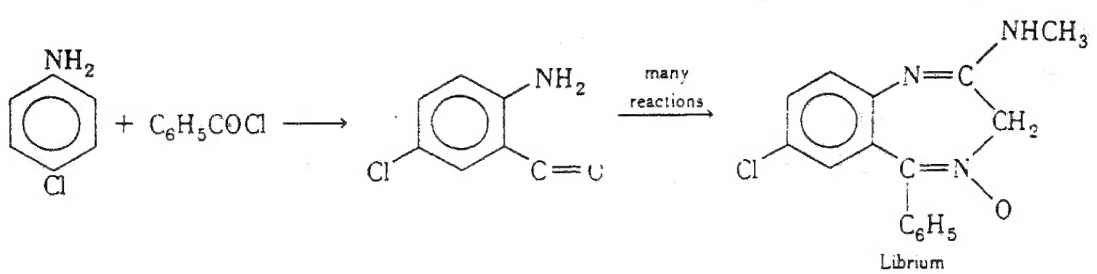
Step 4. Splitting off of the *d*-camphorsulfonic acid using ammonium hydroxide and conversion of the desired α-dextro isomer to the hydrochloride. Frequently, only one of the possible isomers of a compound has any therapeutic activity. In this case, only the dextro isomer is active as an analgesic.

Step 5. Esterification of the α-dextro isomer with propionic anhydride.



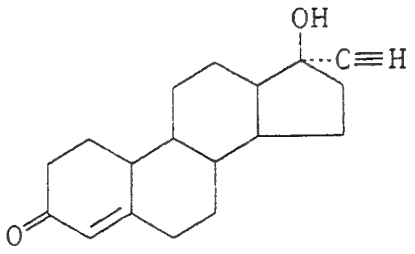
Step 6. Isolation, filtration, drying.

LIBRIUM. In 1976 Librium represented the second largest annual sale of a prescription medicinal. See Table 6.1. Librium (chlordiazepoxide hydrochloride) is made by a complex series of chemical conversions:

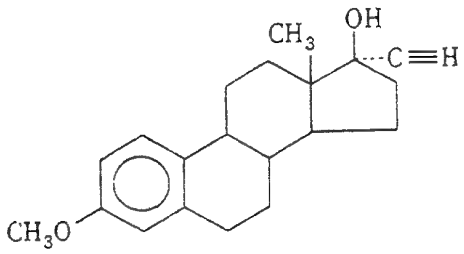


CONTRACEPTIVES. Oral contraceptives are taken daily by millions of women in the United States and throughout the world. Over 30 different products are marketed in the United States alone, in dosages that can be a combination of drugs, a sequence of drugs, or a single drug.

Most of the drugs in oral contraceptives are derived from the general formula:



For instance, one of the drugs, Mestranol, has the folmula:



RADIOISOTOPES IN MEDICINE[32]

Remington devotes chapter 29 to the use and medical applications of radioisotopes.

FERMENTATION AND LIFE PROCESSING FOR ANTIBIOTICS, BIOLOGICALS, HORMONES, AND VITAMINS

Historically the pharmaceutical industry has frequently used materials of plant or animal origin as sources of drugs. It was a logical step, although one a long time in coming, for this industry to employ the life processes of either plants or animals, and especially microorganisms, to produce useful medicaments. This is particularly true of fermentation, in which microorganisms are permitted to grow under controlled conditions to produce valuable and often complex chemicals. Some synthetic or semisynthetic processes can compete with life processes. Both life processes and a chemical synthesis are competitive in the production of riboflavin and chloramphenicol. Vitamin B_{12}[33] is produced by fermentation. See Chap. 4 for general principles of fermentation and for many products made biosynthetically.

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[32]RPS XVI, chap. 29, "Medical Applications of Radioisotopes," p. 458.

[33]Flowchart for Production of Vitamin B_{12} Feed Supplement, *Ind. Eng. Chem.* 46 240 (1954).

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Chapter 6

Pharmaceutical Industry

The human lifespan in the United States has increased since 1900 from 49 years to the present 73+ years. This has been due, in part, to the development of drugs[1] that have controlled or eliminated many diseases that formerly were devastating in their action on humans. The death rate from influenza in the United States per 100,000 population dropped from 102.5 in 1930 to 26.7 in 1978, and from all forms of tuberculosis from 71.1 to 1.0 during the same period. Poliomyelitis has been practically eliminated by the advent of preventive vaccines.

HISTORICAL. The use of drugs to relieve pain and to ward off death is interwoven with the ancient superstition that evil spirits cause disease. The healing powers of mythological personages, particularly of Aesculapius, son of Apollo, were sought in primitive cultures. The Papyrus Ebers, which take us back to the beginning of recorded history in the Nile Valley, contain drug formulas with as many as 35 ingredients, including botanicals, minerals, and animal products. A few of the minerals, such as sulfur, magnesia, and soda, still appear in current pharmacopeias. It was the Greeks, Hippocrates and Galen, who made an effort to approach therapy rationally rather than mystically. Paracelsus, born in 1493, experimented both in the laboratory and the clinic, and may be looked upon as the founder of chemotherapy.

Three centuries later, while Liebig and his students in Germany were synthesizing biologically active compounds, methods for experimental medicine were developed in France by Bernard, Magendie, and others. Although the American pharmaceutical industry had made a modest beginning in 1786, the synthetic organic chemicals ether and chloroform were not used for anesthesia until the 1840s. Three years after the end of the Civil War, the first integrated industrial synthetic organic manufacturing operation was established in the United States.[2] The groundwork for modern pharmaceutical research was begun in 1881 with the establishment of a scientific division of Eli Lilly & Co. The shortage of important drugs, such as sedatives and novocaine, caused by the entry of the United States into World War I, precipitated expansion of the pharmaceutical industry into a successful effort to produce the synthetic chemicals needed.

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[1]The term "drugs" as used in this chapter refers to articles intended for use in the diagnosis, cure, alleviation, treatment, or prevention of disease in humans or animals; Oser (ed.), *Remington's Pharmaceutical Sciences*, vol. 16, 1980, hereinafter cited as RPS XVI.

[2]Albany Aniline Chemical Co. For this and other historical facts, see Tainter and Marcelli, The Rise of Synthetic Drugs in the American Pharmaceutical Industry, *N.Y. Acad. Med.* 35 387–405 (1959).

Developments of insulin, liver extract, and the barbiturates were milestones of the next decade. Sulfa drugs and vitamins were added to many product lines during the 1930s Blood plasma, new antimalarials, and the dramatic development of penicillin resulted from the demands of war. The spectacular surge of new products, which included steroid hormones, tranquilizers, vaccines, and broad- and medium-spectrum antibiotics, came after World War II. The 1970s saw the exciting development of gene splicing to produce new forms of living materials.

USES AND ECONOMICS. The first law in the United States regulating drugs was the Food and Drug Act of 1906, but this act did not require advance testing of new drugs In 1937 the use of ethylene glycol as a vehicle for sulfanilamide caused more than one hundred deaths and led to the 1938 amendment of the FD&C act. This amendment required proof of safety of any new drug *before* it was marketed. The advent of antibiotics led to the 1941 amendment which required certification of safety for each batch of antibiotic. The amendment of 1951 divided drugs into two categories—prescription and over-the-counter (OTC). Prescription drugs are those dispensed to the public by a licensed pharmacist upon the written order (prescription) of a licensed doctor, dentist, or veterinarian and include drugs deemed to be unsafe to be used indiscriminately. OTC drugs are offered for sale by pharmacists or other vendors without a prescription.

Other amendments further restricting the introduction of new drugs and regulating the use of hallucinogenic and narcotic drugs have been enacted. These laws have made the introduction of a drug that can cause deleterious effects upon humans or animals extremely unlikely. However, such safety has some undesirable consequences as it now requires more than seven years to develop and thoroughly test a new drug product. This procedure costs an average of $8 to $10 million. To acquire protection from competition the company developing a new drug must apply for a patent early in the process. Patents are valid for only 17 years, and if 7 years are subtracted for testing before the drug can be marketed, the company has only about 10 years of protection in which to try and recover its $8 million +. This has severely limited the number of new drugs introduced, and only those with a large potential market can be economically considered.[3] Four out of five new drugs never exceed $20 million per year in sales, and a law suit or two can kill the best of them. In 1980 12 new chemical entities were approved by the FDA. The longest remaining patent life was 11 years. 10 months, and 1 of the 12 had no patent protection remaining.

The total U.S. production of bulk medicinal chemicals has increased from 65,000 t in 1964 to 110,000 t in 1980.[3a] Sales of bulk products for 1964 were $643 million and in 1980 $1153 million. These figures do not include finished preparations, such as tablets, capsules, ampules, and the like, which manufacturing pharmacists make from bulk chemicals, antibiotics, and isolates. Antibiotics accounted for 22 percent; gastrointestinal agents, 27 percent; nervous system stimulants and depressants, 25 percent; and vitamins, 17 percent of the 1980 sales.[4] Product shipments in 1981 were valued at $1270 million. In 1981 the U.S. sales of OTC drugs was $5300 million.

The beneficent influence of the pharmaceutical industry on animals for human food is often not recognized. The control of animal diseases by drugs has cut the losses dramatically.

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[3]Burger, Behind the Decline in New Drugs, *Chem. Eng. News* 53 (38) 37 (1965); *Pharm. Mfr. Assoc.* newsletter 23 (31) 6 (1981).

[3a]t = 1000 kg.

[4]*Synthetic Organic Chemicals, 1980, Medicinal Chemicals*, U.S. International Trade Commission, 1981; *U.S. Industrial Outlook*, 1982, U.S. Department of Commerce.

In the early 1950s, American poultry producers suffered annual losses of birds of about 30 percent. Today the usual loss to disease is only about 1 percent. In addition, the use of vitamins, antibiotics, and steroids in animal and poultry feeds has greatly increased the amount of meat produced per unit of feed fed.

The pharmaceutical industry employs 144,800 people in 756 establishments. Of these companies, 463 employed less than 20 people each. The prescription pharmaceutical industry is not dominated by any one firm as can be seen from Table 6.2. The four largest companies accounted for 24 percent of the total. In 1981 the U.S. drug market was valued at $5770 million, and this constituted nearly 21 percent of the world market for drugs.

RESEARCH AND DEVELOPMENT. Members of the Pharmaceutical Manufacturer's Association (PMA), composed of 143 firms who account for approximately 95 percent of the prescription products sold in the United States, reported expenditures of over $1890 million for R&D for 1980, 24 times the amount expended in 1954 and 3 times that of 1970. Government support amounted to only $6.9 million. Research expenditures are a primary factor in determining a company's future share of industry sales and reflect the service rendered to the people. Figure 40.1 shows the R&D expenditures for several years.

CLASSIFICATION

Like most chemicals, pharmaceutical products can be arranged by use, by chemical structure, or by chemical reactions needed to manufacture the product.

Table 6.1 lists sales of OTC drugs and Table 6.2 lists the 50 most prescribed pharmaceutical products. These tables give an overall listing of many of the most useful pharma-

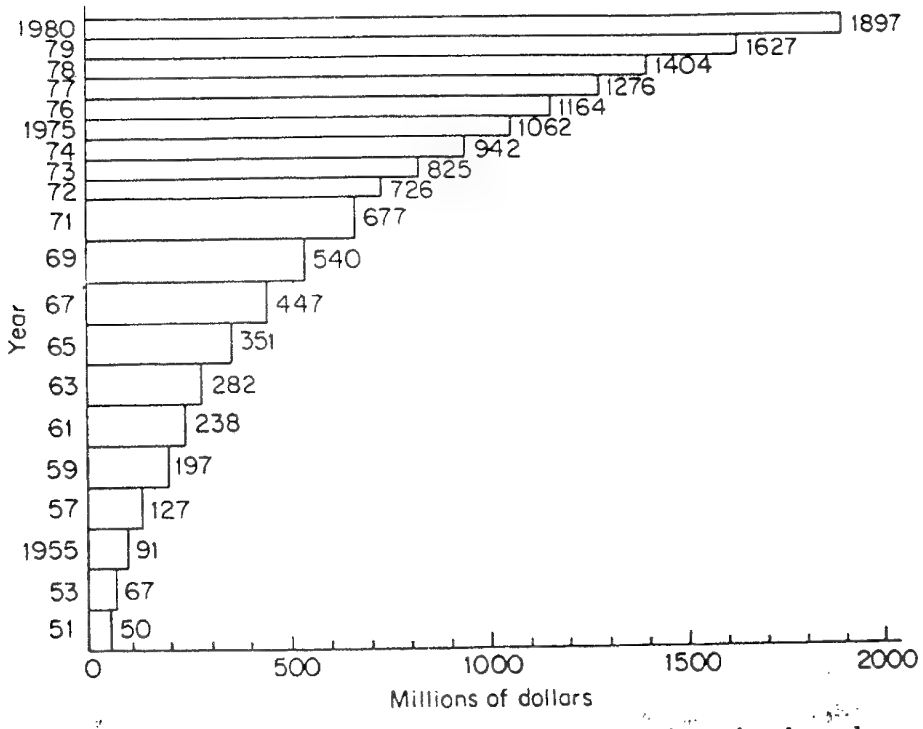


Fig. 6.1. Research and development expenditures for ethical products. *(PMA Annual Survey, 1979–1980.)*

***Table* 6.1** U.S. Retail Sales of OTC Pharmaceutical Products, 1978

	Sales, 10^6 $
Vitamins	950
Cold remedies	1010
Laxatives	360
Analgesics	
Internal	930
External	110
Nonsteroidal contraceptives	130
External antiseptics	120
Antacids	460
Others (burn, eye and contact lens solutions, sleep aids, etc.	1090
Total	4930

***Table* 6.2** Top 50 Most Prescribed Drugs in the United States in 1981

Rank 1981	Rank 1976	Trade Name	Generic Name	Manufacturer°	Therapeutic Class
1	1	Valium†	Diazepam	Roche	Antianxiety
2	16	Inderal†	Propanolol·HCl	Ayerst	Antianginal
3	3	Dyazide‡	Triamterene-hydrochlorothiazide	S K B	Antihypertensive
4	4	Tylenol/codeine	Acetaminophen-codeine phosphate	McNeil	Antipyretic
5	9	Lasix (oral)‡	Furosemide	Hoechst-Roussel	Diuretic
6	7	Motrin‡	Ibuprofen	Upjohn	Antiarthritic
7	16	Lanoxin	Digoxin	B-W	Digitolizer
8	18	Ampicillin‡	Ampicillin	Unspecified	Antibiotic
9	—	Tagamet‡	Cimetidine	S K B	Antiulcer
10	61	Tetracycline†	Tetracycline	Unspecified	Antibiotic
11	22	Penicillin VK	Penicillin VK	Unspecified	Antibiotic
12	35	Dalmane‡	Fluorazepam·HCl	Roche	Sedative
13	n.a.§	Dimetapp‡	Brompheniramine maleate-phenylephrine·HCl	Robins	Decongestant
14	2	Aldomet‡	Methyldopa	M S D	Antihypertensive
15	6	Keflex‡	Cephalexin	Dista	Antibiotic
16	n.a.	Amoxicillin‡	Amoxicillin	Unspecified	Antibiotic
17	8	Hydrochlorothiazide	Hydrochlorothiazide	Unspecified	Diuretic
18	15	Actifed	Triprolidene·HCl pseudoephedrine	B-W	Decongestant
19	83	E.E.S‡	Erythromycin	Abbott	Antibiotic
20	—	Darvocet-N100‡	Propoxyphene napsylate	Lilly	Analgesic
21	32	Erythromycin	Erythromycin	Unspecified	Antibiotic
22	—	HydroDiuril†	Hydrochlorothiazide	M S D	Diuretic
23	—	Slow-K‡	Potassium chloride	Ciba	Electrolyte
24	17	Premarin†	Conjugated estrogens	Ayerst	Estrogenic hormone
25	11	Indocin†	Indomethacin	M S D	Antiarthritic
26	23	Isordil‡	Isosorbide	Ives	Antianginal
27	25	Hygroton	Chlortholidone	USV	Antihypertensive

Table 6.2 Top 50 Most Prescribed Drugs in the United States in 1981 *(continued)*

Rank 1981	Rank 1976	Trade Name	Generic Name	Manufacturer*	Therapeutic Class
28	n.a.	V-cillin†	Penicillin	Lilly	Antibiotic
29	n.a.	Emperin-codeine	Aspirin-codeine phosphate	B-W	Antipyretic, analgesic
30	—	Synthroid	Levothyroxine Sulfate	Flint	Thyroid substitute
31	—	Clinoril‡	Sulindas	M S D	Antiarthritic
32	84	Donnatal†	Phenobarbital	Robins	Antispasmodic
33	40	Prednisone	Prednisone	Unspecified	Adrenocortical steroid
34	34	Dialantin sodium†	Phenytoin sodium	Parke Davis	Anticonvulsant
35	24	Diabinese‡	Chloropropamide	Pfizer	Hypoglycemic
36	19	Benadryl	Diphenhydramine	Pfizer	Antihistamine
37	45	Tranxene‡	Chlorazepate dipotassium	Abbott	Antianxiety
38	20	Amoxil‡	Amoxicillin trihydrate	Beecham	Antibiotic
39	84	Phenobarbital†	Phenobarbital	Unspecified	Sedative
40	—	Lopressor‡	Metoprolol tartrate	Geigy	Antihypertensive
41	71	Naprosyn‡	Naproxen	Syntex	Analgesic
42	5	Elavil	Amitriptyline·HCl	M S D	Antidepressive
43	48	Aldoril‡	Methyldopa-hydrochlorothiazide	M S D	Antihypertensive
44	13	Librium†	Chlorodiazepoxide	Roche	Antianxiety
45	—	Drixoral‡	Dexbromopheniramine maleate-pseudoephedrine sulfate	Schering	Antihistamine
46	30	Fiorinal†	Butalbitol-asprin	Sandoz	Analgesic
47	37	Thyroid	Thyroid	Unspecified	Hormone
48	—	Ativan‡	Lorazepam	Wyeth	Antianxiety
49	47	Antivert	Meclizine·HCl	Roerig	Antihistamine
50	66	Mycolog	Triamcinolone acetamide-gramicidin; neomycin sulfate, nystatin	Squibb	Corticoid steroid

*S K B, Smith Kline Beckman; B-W, Burroughs Wellcome; M S D, Merck, Sharpe & Dohme.

†In the first 50 since 1966.

‡Not in the first 200 in 1965.

§n.a.—not available.

SOURCE: *Pharmacy Times* April 1982.

ceuticals. Remington (RPS XVI) is helpful in presenting important drugs arranged by therapeutic class. In presenting the manufacturing of individual products, however, a chemical conversion classification is in accordance with the arrangement of the rest of this book and is consequently followed hereafter. The pharmaceutical industry employs greater variety and more complicated steps in its manufacturing processes than almost any other section of the chemical process industries. The complexity of the chemical structure of many medicaments probably has a relationship to the even greater complexity of the ailments of human and animal bodies which the products of the pharmaceutical industry are designed to ameliorate. Because of the accompanying complexity in manufacturing processes, it has been difficult to

select the important chemical-conversion step under which to classify the synthesis of an individual chemical.

In the pharmaceutical industry greater emphasis is placed upon the purity of the products than in most other chemical industries, except in certain cases in the nuclear industry (Chap. 21). Another characteristic of the pharmaceutical industry is the use of life processes as a step in the manufacture of some products which have assumed increasing importance in this area: antibiotics, biologicals, hormones, vitamins, and products of fermentation. Many of these pharmaceuticals are classified and presented under fermentation processes in this chapter, but the overall treatment of fermentation is found in Chap. 4. In the early centuries, a large proportion of the products used as medicaments were natural products, mostly derived from plants. It was recognized that such products must be pure, and, in the early decades of the modern pharmaceutical industry, much effort was devoted to separating and purifying the individual products extracted from plants or animals. Extractive methods have been improved by the use of equipment such as the Podbelniak contactor (Fig. 6.6), which allows countercurrent extraction to be performed efficiently and rapidly. This is essential for materials such as penicillin which are sensitive to time, temperature, and acidity. Specialized solvents, such as anhydrous ammonia, various alcohols, esters, and hydrocarbons are also important. Ion-exchange resins facilitate the extraction and purification of individual products such as antibiotics and alkaloids. Sterility and specialized packaging are necessary for many pharmaceuticals.

The U.S. Pharmacopeial Convention sets standards for purity of many prescription and OTC drugs. These standards are listed in the current volume of the U.S. Pharmacopeia, and drugs that meet these standards may use the designation USP. A few other drugs that are not as rigidly standardized are listed in the National Formulary, and drugs that meet these standards may use the letters NF. Many new drugs are not listed in either reference.

As a result of the great amount of research by pharmaceutical firms, many of the old drugs obtained by extraction of natural products have been supplanted by pure synthetic chemicals which may or may not be identical with the natural products. Certain individual drugs still prevail, however, such as morphine, codeine, and reserpine, extracted from plants, for which there is a continued demand on the part of physicians and for which no synthetic counterpart or substitute has been fully accepted.

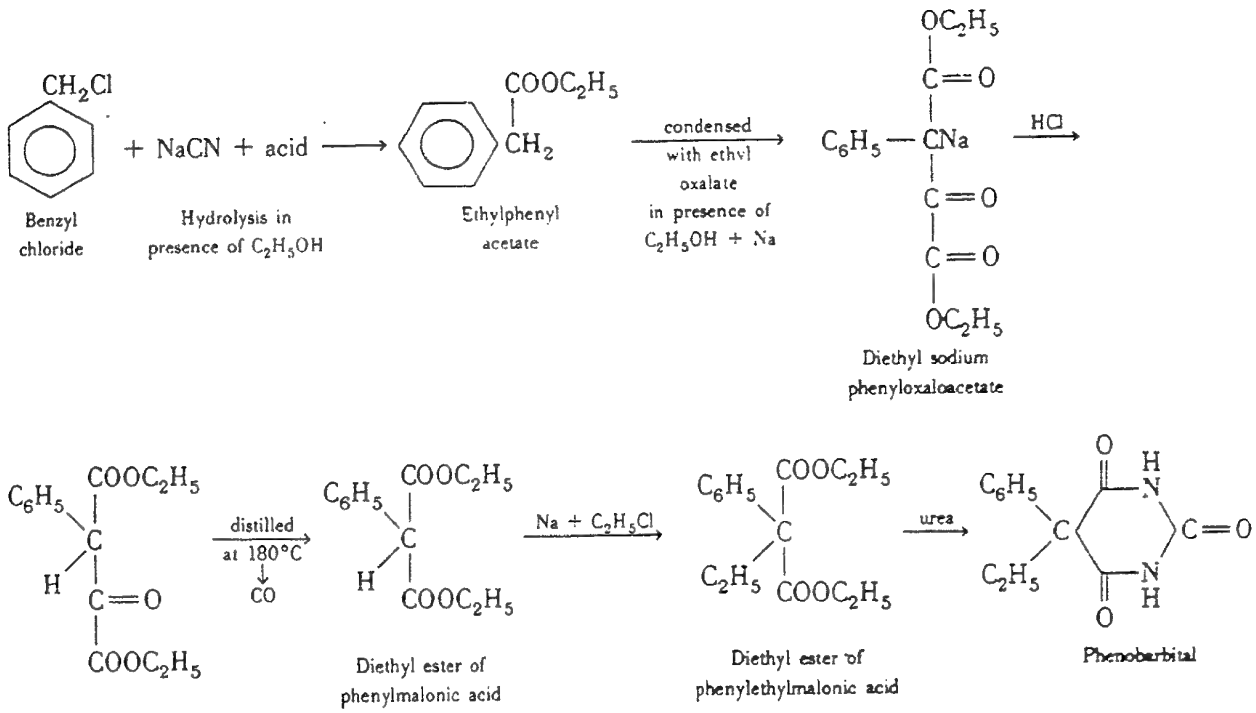
Typical pharmaceutical products are presented from among the thousands manufactured by the industry and used by physicians. They are selected for inclusion in this chapter because of importance, volume produced, or illustrative processes.[5] They are arranged under their outstanding chemical conversion process or under fermentation.

ALKYLATION

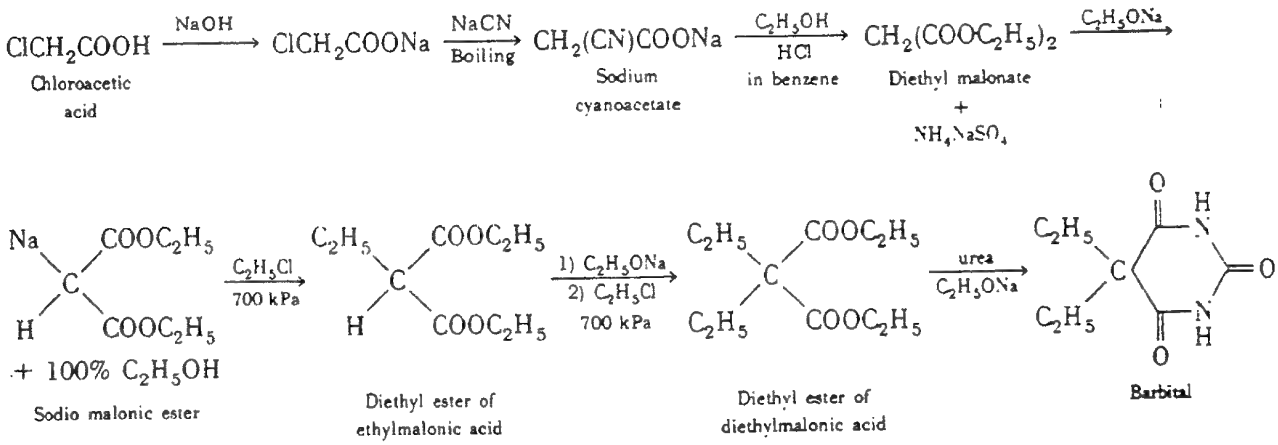
PHENOBARBITAL USP.[6] Phenobarbital, 5-ethyl-5-phenylbarbituric acid, possesses specific usefulness in epilepsy. Like the other barbituric acid derivatives, it is made from phenylethylmalonic diethyl ester, which is condensed with urea to form the product.

[5]RPS XVI gives the best overall short description of the thousands of pharmaceutical products actually employed, together with their various names, methods of production, and clinical properties. Further details can be found in Burger, *Medicinal Chemistry*, 4th ed., 2 vols., Wiley, New York, 1979–1981.

[6]RPS XVI, pp. 998–1003; ECT, 3d ed., vol. 14, 1981, p. 803.



BARBITAL. Barbital, diethylbarbituric acid, is sold under the trade name Veronal. It is the oldest of the long-acting barbiturates and is derived through diethyl malonate.[7]



PROCAINE HYDROCHLORIDE USP. This local anesthetic has long been dispensed under the name novocaine. It is considered to be less toxic than cocaine, and furthermore does not have the danger of habituation. It is used frequently in conjunction with a vasoconstrictor like epinephrine to secure a prolonged anesthetic action. It is obtained by first alkylating ethylenechlorohydrin with diethylamine, which is condensed with *p*-nitrobenzoyl chloride and reduced with tin and hydrochloric acid to obtain procaine.[8]

CODEINE NF AND CODEINE PHOSPHATE USP.[9] Codeine can be isolated from opium, and for many years the supply from this source was sufficient to meet the demand for this sedative

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[7]RPS XVI, p. 1011.

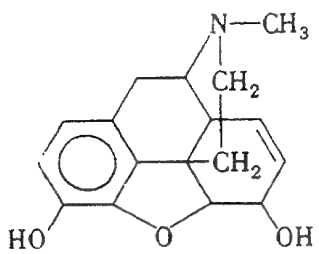
[8]RPS XVI, p. 996.

[9]RPS XVI, p. 1046; Groggins, *Unit Processes in Organic Synthesis*, 5th ed., McGraw-Hill, New York, 1958, p. 846.

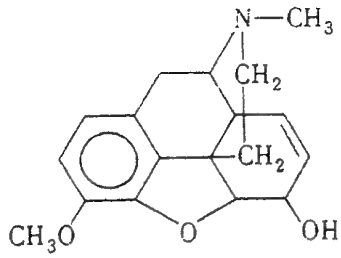
and analgesic drug. Currently demand far exceeds the supply from this source, but morphine (also obtained from opium, but in much larger amounts, 9 parts morphine to 1 part codeine) can be methylated to produce codeine. This is a difficult alkylation as there are three places in the morphine molecule to which a methyl group can be attached: alcoholic hydroxyl, phenolic hydroxyl, and tertiary nitrogen. To direct this alkylation to the phenolic hydroxyl and to reduce alkylation of the tertiary nitrogen, a quaternary nitrogen alkylating agent, phenyltrimethylammonium hydroxide, is employed. This results in yields of 90 to 93 percent codeine and some recovery of unalkylated morphine. The alkylation is carried out with the morphine dissolved in absolute alcohol in the presence of potassium ethylate. The dimethyl aniline and solvents are recovered and reused.

$$\text{morphine} + C_6H_5N(CH_3)_3OH + C_2H_5OK \xrightarrow[410\ kPa]{130°C} \text{codeine} + \underset{\text{Dimethylaniline}}{C_6H_5N(CH_3)_2} + C_2H_5OH + KCl$$

The basis of this reaction is morphine, which is obtained solely by isolation from opium, the dried exudate from the incised, unripe capsule of the opium poppy, *Papaver somniferum*. All the codeine that occurs in opium is isolated. See Morphine under Isolates. The relationship between morphine and codeine can be seen from the structural formulas.



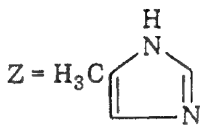
Morphine



Codeine (methylmorphine)

CIMETIDINE. Cimetidine, a highly substituted guanidine, is sold as Tagamet, and is widely used as an antiulcer medication.[10] Annual sales are about $400 million. It acts by blocking the histamine molecules in the stomach from signaling the stomach to secrete acid. Preparation is by the action of a substituted guanidine on an amino-thio compound in the presence of methyl cyanide.

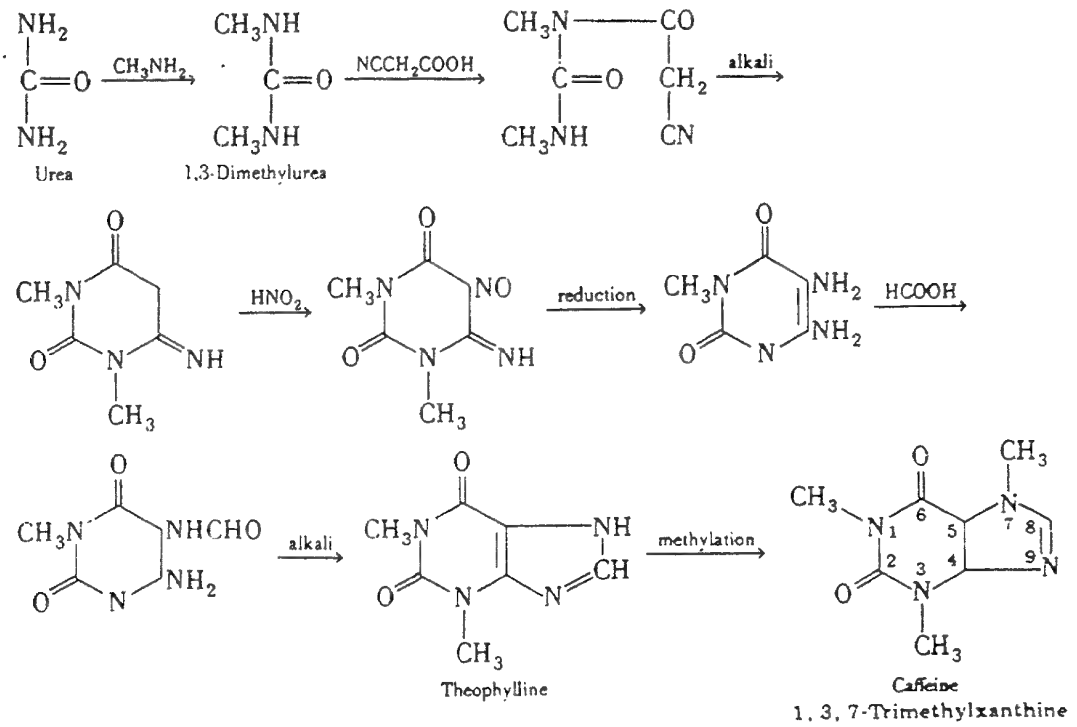
$$CH_3NHC(=NCN)SCH_3 + NH_2CH_2CH_2SCH_2Z \longrightarrow CH_3NHC(=NCN)NHCH_2CH_2SCH_2Z$$



CAFFEINE USP, THEOBROMINE NF, AND THEOPHYLLINE NF. Caffeine, theobromine, and theophylline are xanthine derivatives classified as central nervous stimulants, but differing

[10]RPS XVI, p. 754; New Drugs Tackle Ulcer Victims Excess Acid, *Chem. Eng. News* 60 (15) 24 (1982).

markedly in their properties. They can be extracted from a number of natural sources. Caffeine,[11] the most important, has long been obtained from waste tea and decaffeinization of coffee (see Caffeine under Isolates). The demand for caffeine is large in volume. Over 1.36 $\times$ 10^6 kg of caffeine are produced each year. It can be manufactured synthetically by a number of processes. Some have been employed industrially, for instance, the methylation of theobromine and also total synthesis by methylation and other reactions based upon urea. A typical sequence for the synthetic manufacture of caffeine is:



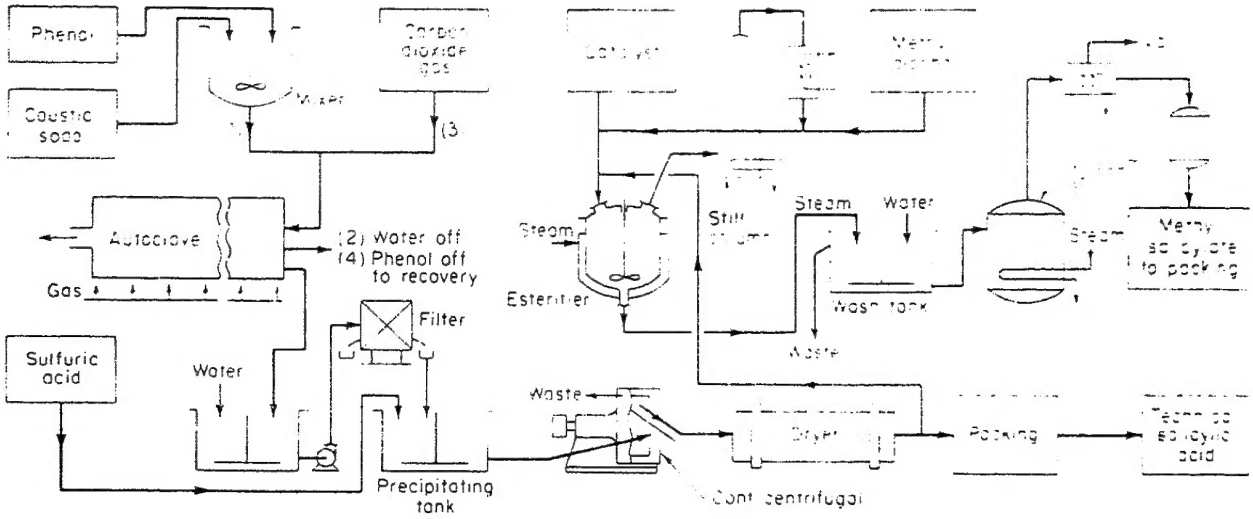
A large demand for caffeine comes from the pharmaceutical industry, but it is also used by the soft-drink industry for mildly stimulating beverages such as Coca Cola, Pepsi Cola, and the other cola drinks. A 600-ml bottle of Coca Cola contains only about one-third the amount of caffeine present in a 150-ml cup of coffee, and about the same amount as in a 150-ml cup of tea. Specifically, this amounts to 33 mg of caffeine in a 600-ml bottle of Coca Cola, whereas a 150-ml cup of tea contains 20 to 50 mg. A 150-ml cup of coffee has 65 to 150 mg.

CARBOXYLATION AND ACETYLATION

SALICYLIC ACID AND DERIVATIVES USP. The chief derivative of salicylic acid that is used as a drug is the methyl acetyl ester, which is known as aspirin. Yearly, over 22 $\times$ 10^3 t of the acid and 19 $\times$ 10^3 t of aspirin are produced. In 1981 the bulk price was $3.63 per kilogram. The manufacture of salicylic acid follows carboxylation by the Schmitt modification of the Kolbe reaction as shown in Fig. 6.2.[12]

[11]RPS XVI, p. 1076.

[12]*Chem. Eng. News* 60 (24) 7 (1982); RPS XVI, p. 1056; Sittig, *Pharmaceutical Manufacturing Encyclopedia*, Noyes, Park Ridge, N.J., 1979.



Reactions: $2C_6H_5OH + 2NaOH \longrightarrow 2C_6H_5ONa + 2H_2O$

$2C_6H_5ONa + CO_2 \longrightarrow ONaC_6H_4COONa + C_6H_5OH$

$ONaC_6H_4COONa + H_2SO_4 \longrightarrow OHC_6H_4COOH + Na_2SO_4$

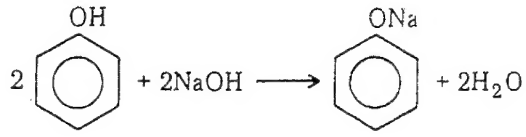
$OHC_6H_4COOH + CH_3OH \longrightarrow OHC_6H_4COOCH_3 + H_2O$

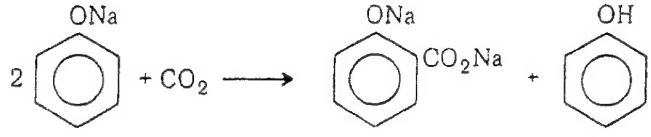
In order to produce 1 t of salicylic acid, the following materials (in kilograms) are required:

Phenol	800	Zinc	10
Caustic soda	350	Zinc sulfate	20
Carbon dioxide	500	Activated carbon	20

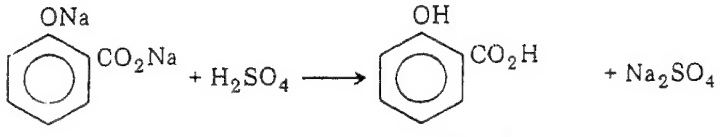
For the production of 1800 kg salicylic acid per day, 5000 kg of steam, 3600 MJ of power, and 53 work-h are required.

Fig. 6.2. Flowchart for salicylic acid and methyl salicylate

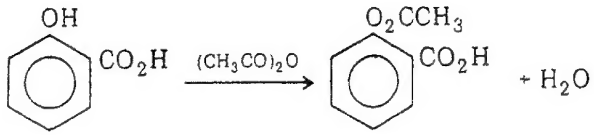




Sodium phenolate Sodium salicylate



Salicylic acid

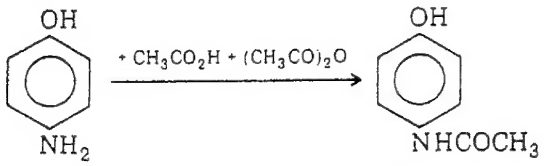


Aspirin

The sodium phenolate must be finely divided and exposed to the action of the CO_2 under pressure and heat. The equipment recommended for this process is a revolving heated ball mill[13] into which the sodium phenolate solution is introduced. By revolving under vacuum and heat (130°C), the sodium phenolate is reduced to a very dry powder, after which the CO_2 is introduced under pressure (700 kPa) and temperature (100°C) to form, first, sodium phenyl carbonate isomerizing to sodium salicylate. This can be dissolved out of the mill, and the salicylic acid decolorized by activated carbon and precipitated by adding sulfuric acid. The salicylic acid is purified by sublimation and can be esterified with methanol and a little sulfuric acid to form methyl salicylate if desired.

To form aspirin, the salicylic acid is refluxed with acetic anhydride in toluene at 88 to 92°C for 20 h. The reaction mixture is then cooled in aluminum cooling tanks, and the acetylsalicylic acid precipitates as large crystals. The crystals are separated either by filtration or centrifugation, washed thoroughly, and dried.

ACETAMINOPHEN USP.[14] Acetaminophen, sold under the tradename Tylenol, is a widely used analgesic and antipyretic that is an OTC drug. Combined with codeine it is one of the top five prescription drugs as shown in Table 6.2. Acetaminophen is prepared by treating *p*-aminophenol with a mixture of glacial acetic acid and acetic anhydride.



Acetaminophen

ACETOPHENETIDINE USP (PHENACETIN). Acetophenetidine, an analgesic and antipyretic, is the ethyl ether of acetaminophen and is prepared from *p*-ethoxyaniline.

CONDENSATION AND CYCLIZATION

The binding together of several molecules by condensation or ring closure to cause cyclization, with or without the splitting out of a smaller molecule, is a very important process employed in the manufacture of a considerable number of pharmaceutical products.

DIAZEPAM USP (VALIUM).[15] Diazepam is a substituted benzodiazepine made by a complex series of reactions, one of which involves cyclization. This compound was introduced between 1955 and 1960, and today is the most prescribed drug in the United States. It is an antianxiety drug, often called a tranquilizer. It is prepared by treating *p*-chloromethylaniline with benzoyl chloride and hydroxylamine to produce the benzophenone oxime. Reaction of the oxime with chloroacetyl chloride in the presence of sodium hydroxide and subsequent reduction yields diazepam.

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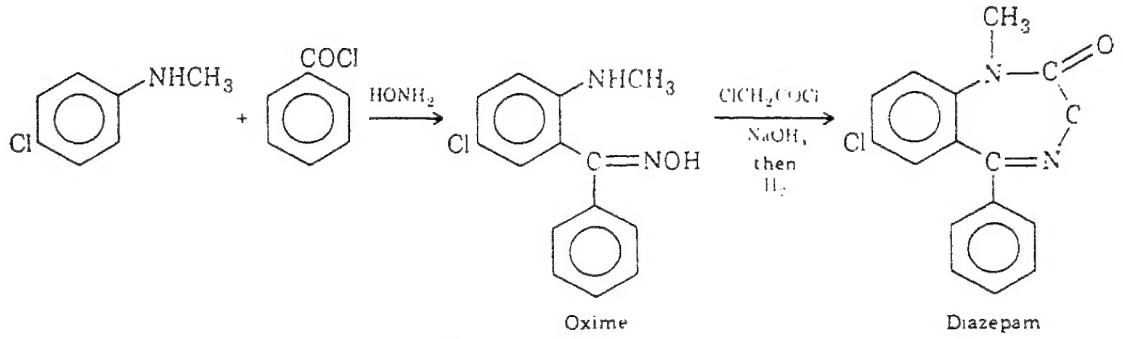
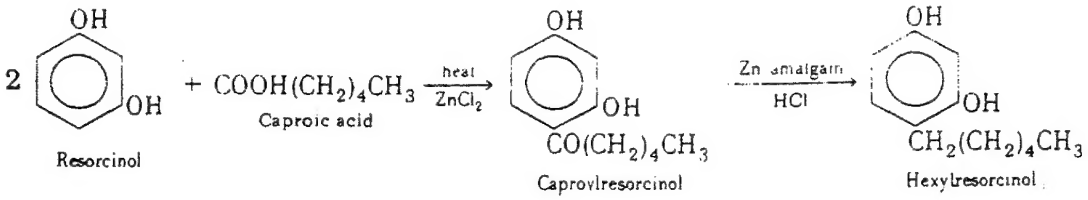
[13]For ball-mill reactor details see Groggins, op. cit., p. 367.

[14]Lednicer and Mitscher, *The Organic Chemistry of Drug Synthesis*, Wiley, New York, 1977.

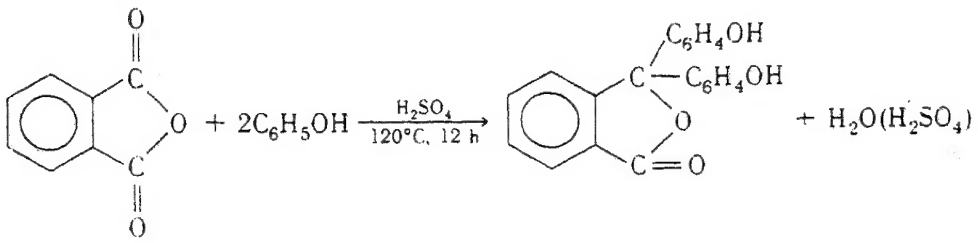
[15]RPS XVI, p. 1007; ECT, 3d ed., vol. 13, 1981, p. 127.



HEXYLRESORCINOL USP (1,3-DIHYDROXY-4-HEXYLBENZENE). Hexylresorcinol has marked germidical properties, and a phenol coefficient of over 50. It is a valued odorless and stainless antiseptic commonly employed in a dilution of 1:1000. It is one of the most efficient anthelmintics against hookworm and the like. In the manufacture of hexylresorcinol,[16] resorcinol and caproic acid are heated with a condensing agent, such as zinc chloride, and the intermediate ketone derivative is formed. This compound is purified by vacuum distillation. After reduction with zinc amalgam and hydrochloric acid (Clemmensen's reduction), impure hexylresorcinol is formed, which can be purified by vacuum distillation. Hexylresorcinol and its analogues were one of the series of related chemicals exhaustively studied to ascertain the relationship between chemical constitution and bactericidal power. It was found that this action increased up to the hexyl derivative and disappeared with the normal octyl derivative, probably because of low solubility. Figure 6.3 plots the atomic weight of the alkyl chain against the phenol coefficient (ratio of antibacterial power measured against the organism *Eberthella typhosa* relative to that of phenol under the same conditions). Simultaneously, with the increase in bactericidal power up to the hexyl derivative, a coincident drop in toxicity was found. Compare Table 40.3 on germicidal activity.



PHENOLPHTHALEIN NE.[17] Phenolphthalein is a widely used cathartic, particularly in proprietary drugs. It is manufactured by adding melted phenol (10 parts) to a cooled solution of phthalic anhydride (5 parts) in concentrated sulfuric acid (4 parts) and heating the mixture 10 to 12 h at 120°C. The hot condensation product is poured into boiling water and boiled with successive changes of hot water. The condensate is then dissolved in warm, dilute caustic soda and precipitated with acetic acid. It may be purified by crystallization from absolute alcohol after treatment with, and being filtering through, activated carbon.



[16]Groggins, op. cit., p. 839; RPS XVI, p. 1181.

[17]RPS XVI, p. 743.

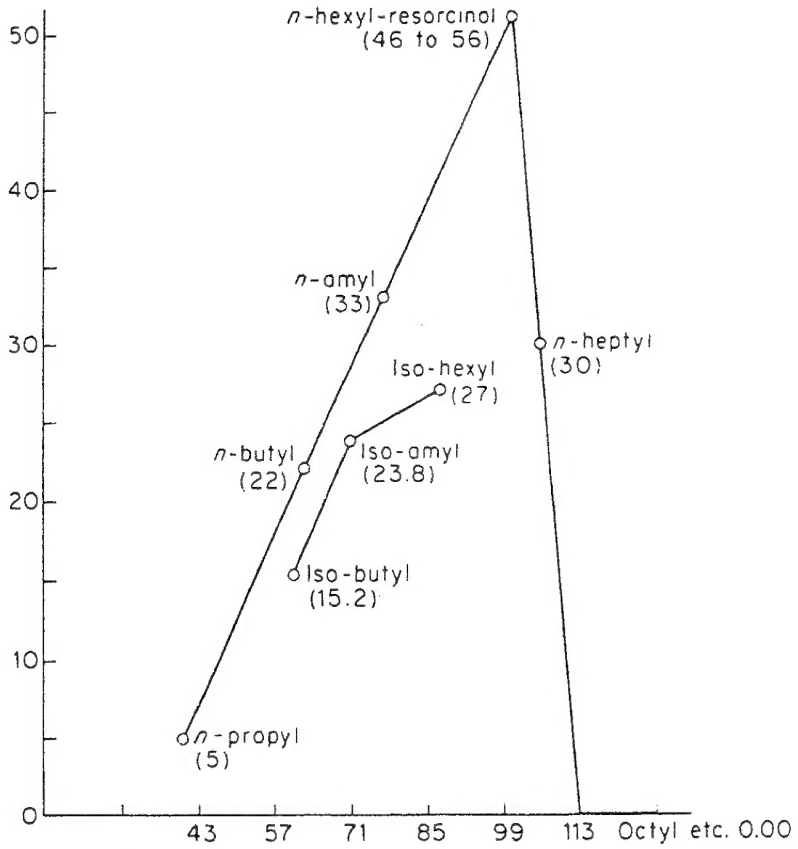
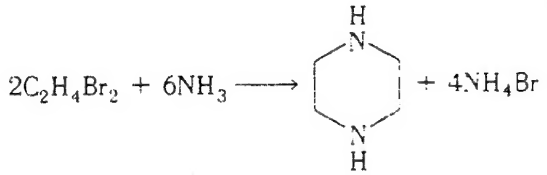


Fig. 6.3. Bacterial activity of the alkylresorcinols. The curve is obtained by plotting the phenol coefficients (U.S. Hygienic Laboratory technique) as ordinates against the sum of the atomic weights of the atoms in the alkyl chains as abscissas. [*Dohm, Cox, and Miller, J. Am. Chem. Soc.*, 48 *1688 (1962); Groggins, Unit Processes in Organic Synthesis, 5th ed., McGraw-Hill, New York, 1958, p. 389.*]

PIPERAZINE CITRATE USP.[18] Piperazine citrate is used as an anthelmintic in the treatment of infections caused by pinworms and roundworms. It is also employed by veterinarians against various worms infecting domestic animals, including chickens. The U.S. International Trade Commission reported production in 1980 of 1.8×10^3 t and a sales value of about $6.5 million. Piperazine is prepared by the cyclization of ethylene dibromide with alcoholic ammonia at 100°C. The citrate is formed in aqueous solution and crystallized out.



THIAMINE HYDROCHLORIDE USP, VITAMIN B_1.[19] This antineuritic vitamin is essential for bodily growth and the prevention of beriberi. Although thiamine is widely distributed in many foods, most commercially available quantities are obtained by the condensation of 6-amino-5-bromomethyl-2-methylpyrimidine hydrobromide with 5-(hydroxytethyl)-4-meth-

[18]RPS XVI, p. 1182.

[19]RPS XVI, p. 968.